Current Research in Translational Medicine xxx (2016) xxx–xxx

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Original article

Major bleeding complications in patients treated with direct oral anticoagulants: One-year observational study in a Paris Hospital

L. Deville [a,1], M. Konan [b,c,1], A. Hij [b], L. Goldwirt [d], O. Peyrony [e], F. Fieux [f], P. Faure [a], I. Madelaine [a], S. Villiers [g], D. Farge-Bancel [b], C. Frère [h,i,*]

[a] Service de pharmacie, hôpital Saint-Louis, Assistance publique–Hôpitaux de Paris, 1, avenue Claude-Vellefaux, 75010 Paris, France
[b] Unité de médecine interne et pathologie vasculaire, hôpital Saint-Louis, Assistance publique–Hôpitaux de Paris, 1, avenue Claude-Vellefaux, 75010 Paris, France
[c] Service de médecine interne, CHU de Treichville, Abidjan, Côte d'Ivoire
[d] Unité de pharmacologie, hôpital Saint-Louis, Assistance publique–Hôpitaux de Paris, 1, avenue Claude-Vellefaux, 75010 Paris, France
[e] Service des urgences, hôpital Saint-Louis, Assistance publique–Hôpitaux de Paris, 1, avenue Claude-Vellefaux, 75010 Paris, France
[f] Service de réanimation chirurgicale, hôpital Saint-Louis, Assistance publique–Hôpitaux de Paris, 1, avenue Claude-Vellefaux, 75010 Paris, France
[g] Service d'anesthésie réanimation, hôpital Saint-Louis, Assistance publique–Hôpitaux de Paris, 1, avenue Claude-Vellefaux, 75010 Paris, France
[h] Service d'hématologie biologique, CHU Timone, Assistance publique–Hôpitaux de Marseille, 264, rue Saint-Pierre, 13385 Marseille, France
[i] Inserm UMRS 1076, VRCM, Aix-Marseille université, 13385 Marseille, France

ARTICLE INFO

Article history:
Received 11 January 2016
Accepted 12 February 2016
Available online xxx

Keywords:
Direct oral anticoagulants
Major hemorrhage
Contraindications
Precautions for use
Risk/benefit ratio

ABSTRACT

Direct oral anticoagulants (DAOC) are indicated for the treatment of venous thromboembolism and the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation. Given their advantages and friendly use for patient, the prescription of long term DOAC therapy has rapidly increased both as first line treatment while initiating anticoagulation and as a substitute to vitamins K antagonist (VKA) in poorly controlled patients. However, DOAC therapy can also be associated with significant bleeding complications, and in the absence of specific antidote at disposal, treatment of serious hemorrhagic complications under DOAC remains complex. We report and discuss herein five cases of major hemorrhagic complications under DOAC, which were reported to the pharmacological surveillance department over one year at Saint-Louis University Hospital (Paris, France). We further discuss the need for careful assessment of the risk/benefit ratio at time of starting DOAC therapy in daily clinical practice.

1. Introduction

The prescription of direct oral anticoagulants (DOAC) has increased since 2008 as an alternative to vitamin K antagonists (VKA), which still remain the most commonly prescribed oral anticoagulant drugs [1]. Several large double-blind randomized controlled trials (RCTs) have validated the efficacy and the safety of DOAC use as compared to VKA for the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (NVAF) associated with at least one thrombotic risk factor, as well as for the treatment of venous thromboembolism (VTE). In France, three DOAC drugs (dabigatran, rivaroxaban and apixaban) have been successively released on the market and allowed for prescription by the health authorities.

The use of DOAC, which are synthetic molecules with specific mechanisms of action, is much easier as compared to the use of VKA, for the following reasons:

- a fixed oral daily dose can be prescribed;
- the pharmacokinetics/pharmacodynamics profile is predictable and does not necessitate biological monitoring;
- the therapeutic window is large;
- the half-life is short;
- drug interactions are rare.

The efficacy and safety of DOAC have been evaluated in a number of phase III RCTs. A meta-analysis of the RE-LY (dabigatran vs VKA, $n = 18113$), [2] ROCKET-AF (rivaroxaban vs AVK, $n = 14,264$), [3] ARISTOTLE (apixaban vs VKA, $n = 18,201$), [4] and ENGAGE-AF-TIMI48 (edoxaban vs VKA, $n = 21,105$) [5]

* Corresponding author. Service d'hématologie biologique, CHU Timone, Assistance publique–Hôpitaux de Marseille, 264, rue Saint-Pierre, 13385 Marseille, France.
E-mail address: Corinne.Frere@ap-hm.fr (C. Frère).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.retram.2016.02.003
2452-3186/

RCTs allowed to analyze 71,683 patients with NVAF, of which 59% were treated by DOAC [6]. Results demonstrated a significant reduction risk in intracranial hemorrhage with DOAC as compared with VKA (RR, 0.48; 95% CI, 0.30–0.59; $P < 0.0001$), but the difference was not significant when comparing the risk of total major bleeding (RR, 0.86; 95% CI, 0.73–1.00; $P = 0.06$) [6]. A few months after the introduction on the market of dabigatran, the United States Food and Drug Administration (FDA) reminded prescribers the need of specific attention concerning the rate of serious hemorrhagic complications reported under DOAC, which was higher than initially expected, as based on the RE-LY study [7]. However, the risk of fatal or major bleeding remains the most concerning complications under oral anticoagulation whether patients are under DOAC or VKA [8–14]. Hemorrhagic complications under DOAC, however, appear frequently related to misusage of the drug and to non-compliance with the good clinical practice prescription rules.

We report and discuss herein the five cases of major hemorrhagic complications under DOAC that were declared to pharmacovigilance department and supported at Saint-Louis University Paris Hospital over a one-year period. Such observations and analysis allow to underline the need for carefully assessment of the risk/benefit ratio at the time of initiating DOAC therapy in daily clinical practice.

2. Patients and methods

This observational study included all cases of major hemorrhagic complications under DOAC treated at Saint-Louis University Hospital from June 2013 to July 2014 as declared to the pharmacovigilance department.

The standard definition of major bleeding in non-surgical patients according to the ISTH subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) is defined as having a symptomatic presentation and [15]:

- fatal bleeding;
- and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with a compartment syndrome;
- and/or bleeding causing a fall in hemoglobin level $\geq 20\ g{\cdot}L^{-1}$ or more, or leading to transfusion of two or more units of whole blood red cells.

Patients' clinical and biological characteristics, as well as simultaneous treatments given at time of bleeding were retrospectively collected from hospital case report charts.

3. Results

From June 2013 to July 2014, 5 cases (3 males, 2 females) of major bleeding complications under DOAC were reported to Saint-Louis Hospital pharmacovigilance center. Their main characteristics, the type of hemorrhage, treatment support and clinical evolution are summarized in Table 1. The complications were

Table 1
Patient main characteristics.

Patient number	1	2	3	4	5
Gender	Male	Female	Female	Male	Male
Age (years)	78	86	80	69	78
Weight (kg)	82	51		93	103
Size (cm)	170	163		180	
Body Mass Index	28,37	19		28	
Department	Department of Emergency Medicine	Department of Internal Medicine	Department of Emergency Medicine	Department of Anesthesiology	Department of Reanimation
Type of DOAC	Dabigatran	Dabigatran	Dabigatran	Rivaroxaban	Rivaroxaban
Dose	110 mg × 1/day	110 mg × 2/day	110 mg × 2/day	20 mg/day	15 mg/day
DOAC indication	Atrial flutter	Non-valvular atrial fibrillation	Non-valvular atrial fibrillation	Non-valvular atrial fibrillation	Non-valvular atrial fibrillation
DOAC exposure time	5 months	18 months	1 month	Unknown	24 months
Antécédents	Hypertrophic and dilated cardiomyopathy	Arterial Hypertension Intracranial Bleeding	Stroke Heart failure	Peritonitis, appendicitis Arterial Hypertension	Arterial Hypertension Cognitive disorders Hemorrhagic shock with VKAs
Comedications	Amiodarone 200: 1-0-0 Béclométasone 100 µg: 1-0-1 Bisoprolol 2,5 mg: 1 -0 -0 Perindopril 4 mg: 1-0-0 Spironolactone 75 mg: 1-0-0 Trospium 20 mg: 0-0-1	Bisoprolol 5 mg: 1-0-0 Furosemide 40 mg: 1-0-0 Hydrochlorothiazide + Enalapril 12,5 mg/20 mg: 1-0-0 Levothyroxine 100 µg: 1-0-0	Amiodarone 1/2 cp 3fois par semaine Bisoprolol 2,5 mg: 1-0-0 Furosemide 20 mg: 1-0-0	Irbesartan 150 mg: 1-0-0 Digoxine 0,125: 1-0-0 Nebivolol 5 mg: 1-0-0	Carbonate calcium 500 mg: 2-2-2 Escitalopram 10 mg: 1-0-0
Blood pressure (mmHg)	94/55	161/99	110/69	184/101	114/70
Heart rate (per minute)	71	82	76	65	70
Glasgow Score	15	15	15	6	3
Creatinine ($\mu mol{\cdot}L^{-1}$)	94	66	63	69	63
Creatinine clearance ($mL{\cdot}min^{-1}$)	67	43	50	118	125
Hb ($g{\cdot}L^{-1}$)	64	129	85	120	136
Activated partial thromboplastin time (ratio patient/normal value)	1.67	1.57	2.13	1.12	1
Glycemia ($g{\cdot}L^{-1}$)	4.79	5.09		6.4	8.28
Number of red cell concentrates (RCC)	8	None	2	None	None
CHAD2S2-VASc Score	4	6	4	2	3
Type of major bleeding	Gastrointestinal bleeding	Intracranial bleeding	Gastrointestinal bleeding	Intracranial bleeding	Subdural hematoma
Evolution	Prolonged hospitalization	Prolonged hospitalization	Prolonged hospitalization	Death	Death

Please cite this article in press as: Deville L, et al. Major bleeding complications in patients treated with direct oral anticoagulants: One-year observational study in a Paris Hospital. Curr Res Transl Med (2016), http://dx.doi.org/10.1016/j.retram.2016.02.003